REMARKS

1. Preliminary Matters

a. Status of the Claims

Claims 21, 44, and 50-53 are pending and under active consideration in this application.

b. Provisional Nonstatutory Obviousness-Type Double Patenting Rejection

On pages 2-5 of the Office Action, the Examiner provisionally rejects claims 21, 44, and 50-53 on grounds of nonstatutory obviousness-type double patenting.

(1) Over U.S. App. No. 10/535,164

The Examiner asserts that these claims are allegedly unpatentable over claims 1-3, 10, 13 and 14 of copending U.S. App. No. 10/535,164 (the "'164 Application"). However, the pending claims of the '164 Application are directed to nucleic acids related to SEQ ID NO: 15215, which is different from the instantly claimed SEQ ID NOs: 1916, 1917, 4641, and 4642. Accordingly, the claims of the '164 Application do not anticipate the instant claims. Applicant respectfully requests that the Examiner reconsider and withdraw the obviousness-type double patenting rejection over the claims of the '164 Application.

(2) Over U.S. App. No. 10/605,838

The Examiner also alleges that the instant claims are unpatentable over claims 1-3, 8, 11, and 12 of copending U.S. App. No. 10/605,838 (the "'838 Application"). The instant application was filed on August 29, 2003, which predates the filing date of October 30, 2003 for the '838 Application. Because the instant application was filed earlier, Applicant respectfully requests that the obviousness-type double patenting rejection over the '838 Application be withdrawn pursuant to M.P.E.P. § 804.I.B1.

(3) Over Other Copending Applications

The Examiner further alleges that obviousness-type double patenting rejections might be applied over U.S. App. Nos. 11/511,035; 11/384,049; 11/709,691; 10/708,953; 10/536,560; 10/605,840; 10/709,572; 10/709,739; 11/130,649; 10/604,985; 10/605,923; 10/707,003; 10/707,147; 10/707,975; 10/708,204; 10/708,951; 10/708,952; 11/418,870; 10/604,726; 10/604,926; 10/604,943; or 10/604,945 (the "Copending Applications"). Applicant respectfully submits that it is not possible to perform a proper analysis of this double patenting rejection. This is because it is not clear which claims or subject matter of the instant application are patentably indistinct over which claims or subject matter of the Copending Applications. Applicant therefore requests clarification of the rejection over the Copending Applications. Upon clarification, Applicant may consider amending claims in the Copending Applications or filing a terminal disclaimer for the instant application if the rejection is maintained when one or more claims in the instant application are in condition for allowance.

2. Patentability Remarks

a. 35 U.S.C. § 101

On pages 5-10, the Examiner rejects claims 21, 44, and 50-53 under 35 U.S.C. § 101 because the claims allegedly are not supported by either a credible asserted utility or a well established utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See Fisher*, 421 F.3d at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the claimed miRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The *Fisher* application did not disclose the location of the ESTs in the genome or the function of the underlying genes. *Fisher* asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) providing a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Fisher*, 421 F.3d at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids may be used to target and modulate expression of **specific** gene transcripts. Figure 1931D/1, Table 2, lines 132,628-132,632, and Table 1, lines 13,415-13,419 of the application disclose that the claimed miRNA-related sequences specifically target mRNA transcripts of the target gene COL6A1. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids

regulate the translation of mRNAs from the **specific target gene COL6A1**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating COL6A1.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, it must be shown that the asserted use of the claimed invention has a significant and presently available benefit to the public. *See Id.* at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a substantial utility for the claimed miRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, it was admitted that the underlying genes for the ESTs had no known function. *Fisher* argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, *Fisher* failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Fisher*, 421 F.3d at 1373, *quoting Brenner v. Manson*, 383 U.S. 519 (1966).

In contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of COL6A1. *Instant Application,* Figure 1931D/1 and Table 2, lines 132,628-132,632. In addition, COL6A1 is known to be a subunit of the extracellular matrix protein collagen VI. *See* Lamandé SR, *et al.*, *Jo Biol Chem* 1999;274(31):21817-22 ("Lamandé"). COL6A1 protein interacts with two other collagen VI subunits, which are assembled into antiparallel overlapping dimers and tetramers that are then secreted into the extracellular matrix. *Id.* Mutations in the COL6A1 gene are haploinsufficient and can cause defects in defective intracellular assembly and a matrix with reduced amounts of structurally normal collagen VI. *Id.* This can result in Bethlem myopathy, which is characterized by childhood onset of generalized muscle weakness and wasting, and contractures of multiple joints. *Id.* Collagen VI subunits can be expressed in human bone cells *in vitro* to affect collagen VI assembly and secretion into the extracellular matrix. *Id.* Because haploinsufficiency of COL6A1–a ~50% reduction in the expression level of the gene–is known to have deleterious effects associated with reduced amounts of functional collagen VI, COL6A1 expression could be modulated *in vitro* to alter collagen VI assembly and secretion.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. Such benefits are the ability to modulate the expression of COL6A1 in order to alter collagen VI assembly and secretion. In view of the application providing particular targets of known function for the claimed miRNA-related nucleic acids, Applicant respectfully

submits that the specific and substantial utility requirements are satisfied in accordance of *Fisher* and *Guidelines*.

(3) Credible Utility

On page 6 of the Office Action, the Examiner alleges that the specification provides no direct or indirect evidence for any credible utility for the RNAs encoded by instantly claimed SEQ ID NOs: 1916, 1917, 4641, or 4642. On page 7, the Examiner asserts that there is no evidence suggesting that the claimed nucleic acids are expressed in any cell whatsoever. On page 9, the Examiner further asserts that applicant has presented no evidence that validation techniques such as miRNA overexpression have been carried out with regard to the instantly claimed sequences. Applicant submits herewith experimental evidence that the claimed Epstein-Barr Virus-related nucleic acids regulate the asserted target COL6A1.

Applicant submits that if Epstein-Barr virus does not express the claimed nucleic acids and these nucleic acids do not target COL6A1, then one of skill would predict that expression of Epstein-Barr virus would have no effect on COL6A1 expression. On the other hand, if the Epstein-Barr virus expresses the claimed nucleic acids, and these nucleic acids inhibit expression of COL6A1, as Applicant has asserted, then one of skill would expect that infecting a cell with Epstein-Barr virus would lead to a decrease in the level of COL6A1.

Applicant used quantitative reverse transcription PCR to test this by comparing the level of COL6A1 mRNA in peripheral blood mononuclear cells (PBMC), which do not normally express ebv-miR-BART1-3P (SEQ ID NO: 4642), to the level in PBMC that have been infected with EBV (See Appendix for further details). Uninfected PBMC had a Ct value of over 22 for COL6A1 mRNA, while EBV-infected PBMC had Ct of less than 16. Thus, uninfected PBMC had 120 times more COL6A1 mRNA compared to infected PBMC. Accordingly, these results are consistent with those one of skill would predict for a virus that expresses a miRNA (ebv-miR-BART1-3P; SEQ ID NO: 4642), which targets COL6A1 miRNA. Applicant submits that this is evidence that the claimed nucleic acids are expressed by EBV and regulate the asserted target COL6A1. In view of the foregoing evidence of specific, substantial, and credible utility for the claimed nucleic acid, Applicant requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 101.

b. 35 U.S.C. § 112, first paragraph

On page 10 of the Office Action, the Examiner rejects claims 21, 44, and 50-53 under 35 U.S.C. § 112, first paragraph because the claimed subject matter allegedly lacks utility. Applicant disagrees in view of the foregoing evidence that the claimed nucleic acids are supported by a specific, substantial, and credible utility. Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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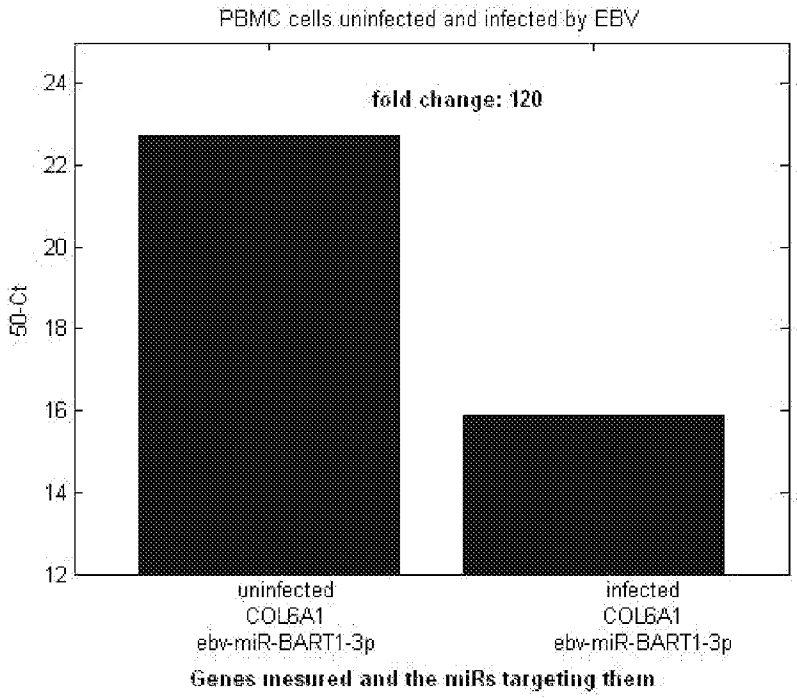
APPENDIX

In order to validate COL6A1 (SEQ ID NO: 7584) as a target of ebv-mir-BART1-3P (SEQ ID NO: 4642), Applicant infected Peripheral Blood Mononuclear Cells (PBMC), which do not express ebv-miR-BART1-3P with Epstein-Barr Virus (EBV) virus. After infection RNA was isolated, the mRNA levels of COL6A1 were quantified using specific primers by SYBR RT-qPCR method (see below).

Measuring the amount of initial mRNA was based on the observation that the amount of cDNA generated from the mRNA doubles with every cycle of PCR. Therefore, after N cycles, there is 2N times as much. In order to quantify the initial amount of mRNA, the cycle number at which the increase in fluorescence (and thus the amount of cDNA) was exponential, was measured. A threshold at this level of fluorescence was set. This threshold is indicated as the cycle threshold, or Ct. To compare the differences in quantity between a specific mRNA in two different samples, the Ct was calculated in each of the samples, and the delta Ct (dCt) was calculated. The fold-change between the amount of mRNA in the two samples was represented by 2dCt.

The expression of COL6A1 in infected and non infected PBMC cells is presented in Figure 1.

Figure 1.



The levels of COL6A1 mRNA were 120 fold higher in infected cells which expressed ebv-miR-BART1-3P as compared to non infected cells which did not express ebv-miR-BART1-3P. Figure 1

shows that infection with EBV virus that expressed ebv-miR-BART1-3P caused a significant increase in the level of COL6A1 mRNA, indicating that this miRNA regulates this gene's expression.

Viral miRs Target Validation

Samples

Peripheral Blood Mononuclear Cells were infected with Epstein-Barr Virus (EBV). RNA extracted from infected and non-infected control cells was used for quantification of ebv-miR-BART1-3p target mRNA (COL6A1) by quantitative RT-PCR. RNA of cells virally infected, and RNA of non-infected cells were used for mRNA quantification by RT-PCR.

Sample (RNA)	miRNA	Target
Peripheral Blood Mononuclear Cells – uninfected control	Ebv miR-BART1-3p	COL6A1
Peripheral Blood Mononuclear Cells infected with EBV		

Reverse Transcription

1µg of total RNA was reverse-transcribed using Superscript II.

Quantification by RT-qPCR

mRNA was quantified by real-time-qPCR SYBR Green method, using 7500 Fast Real time PCR system, AB applied Bio-systems. Each mRNA was tested using two primer pairs, and was done in triplicates. Ct values were normalized to TBP and RPS20 as house keeping genes.

The following primers were used for mRNA quantification:

Primer_id	sequence	Gene name
16339-Fwd	GCTGGTCAAGGAGAACTATGC	COL6A1
16340-Rev	TGGTGGTGTCAAAGTTGTGG	COL6A1
16341-Fwd	CAGCTCAATGTCATTTCTTGC	COL6A1
16342-Fwd	CCATGAAATACACGCTGTGC	SNPH
16343-Rev	ACTCCTCCTCAATCCAGTCC	SNPH
16344-Fwd	CAGAAGGAGGTGTGCATCC	SNPH
16345-Rev	GCTTGAGCTGCTTGATCTCC	SNPH

	Primers for Target	
House keeping	Fwd	Rev
TBP	TATAATCCCAAGCGGTTTGC	CACAGCTCCCCACCATATTC
RPS20	TATAATCCCAAGCGGTTTGC	CACAGCTCCCCACCATATTC

Normalization was done by subtracting the Ct value of the geometric mean of two house keeping gene TBP and RPS20. Ct values were determined using a default threshold of 0.2 in the 7500 Fast Real time PCR system, by ABI.